CLAIMS

We claim:

1. A method of treating a lesion or cavity in a tissue comprising filling said lesion or cavity with a solid implant along with an injectable cell-containing formulation.

2. The method of Claim 1 wherein the solid implant contains cells.

3. The method of Claim 1 wherein the solid implant and injectable formulation are implanted into a cavity or an anatomic site requiring repair or replacement of missing or diseased tissue.

4. The method of Claim 2 wherein the cells in the solid implant are chondrocytes.

5. The method of Claim 2 wherein the cells are extracellular matrix producing cells selected from chondrocytes; osteoblasts; keratinocytes; fibroblasts derived from skin, tendon, ligament, meniscus, temporalmandibular joint or intervertebral joint, disk or any other connective tissue; stem cells derived from skin, tendon, ligament, meniscus, disk or any other connective tissue; stem cells derived from bone marrow stroma, muscle, skin or other stem cell-containing tissue; embryonic stem cells; or combinations of these cells that may be seeded onto the microcarrier.

6. The method of Claim 2 wherein the solid implant is made by culturing cells on biodegradable microcarriers.

7. The method of Claim 6 wherein the microcarrier is selected from inorganic materials selected from calcium phosphates, calcium carbonates, calcium sulfates or combinations of these

materials; organic materials including biopolymers; synthetic polymeric materials; particles of tissues; or chemically modified derivatives of these materials.

8. The method of Claim 7 wherein the microcarrier is selected from inorganic materials selected from calcium phosphates, calcium carbonates, calcium sulfates or combinations of these materials; organic materials including biopolymers selected from collagen, gelatin, hyaluronic acid or chemically derived modifications of hyaluronic acid, chitin, chitosan or chitosan derivatives, fibrin, dextran, agarose, or calcium alginate, or synthetic polymeric materials selected from polylactic acid, polyglycolic acid or copolymers or combinations of the two, polyurethanes, polycarbonates, polycaprolactones, hydrogels such as polyacrylates, polyvinyl alcohols, polyethylene glycols, or polyethyleneimines; or particles of tissues selected from bone or demineralized bone, cartilage, tendon, ligament, fascia, intestinal mucosa or other connective tissues, or chemically modified derivatives of these materials.

9. The method of Claim 6 wherein cell-microcarrier aggregates are further cultured inside a mold which has been shaped to configure the geometry of the area of the body receiving the cells for implantation.

10. The method of Claim 6 wherein the mold is shaped to produce a form that can be cut or modified to a desired shape at the time of implantation.

11. The method of claim 6 wherein the culturing of said cells takes place over one to five weeks.

12. The method of claim 6 wherein the cells are seeded onto the microcarrier at a density of 1 to 4 x 10^3 cells/cm^2.

13. The method of Claim 1 wherein the solid implant is made by culturing cells on a porous biodegradable scaffold.

14. The method of Claim 13 wherein the scaffold is selected from inorganic materials, organic materials including biopolymers, synthetic polymeric materials or particles of tissues.

15. The method of Claim 13 wherein the scaffold is selected from inorganic materials selected from calcium phosphates, calcium carbonates, calcium sulfates or combinations of these materials; organic materials including biopolymers selected from collagen, gelatin, hyaluronic acid or chemically derived modifications of hyaluronic acid, chitin, chitosan or chitosan derivatives, fibrin, dextran, agarose, or calcium alginate, or synthetic polymeric materials selected from polylactic acid, polyglycolic acid or copolymers or combinations of the two, polyurethanes, polycarbonates, polycaprolactones, hydrogels selected from polyacrylates, polyvinyl alcohols, polyethylene glycols, or polyethyleneimines; or particles of tissues selected from bone or demineralized bone, cartilage, tendon, ligament, fascia, intestinal mucosa or other connective tissues, or chemically modified derivatives of these materials.

16. The method of Claim 13 wherein the scaffold has been shaped to configure the geometry of the area of the body receiving the cells for implantation.

17. The method of Claim 13 wherein the scaffold is shaped to produce a form that can be cut or modified to a desired shape at the time of implantation.

18. The method of Claim 1 wherein the solid implant is a biodegradable scaffold.

19. The method of Claim 18 wherein the scaffold is selected from inorganic materials, organic materials, including biopolymers, synthetic polymeric materials, particles of tissues, or chemically modified derivatives of these materials.

20. The method of Claim 18 wherein the scaffold is selected from inorganic materials selected from calcium phosphates, calcium carbonates, calcium sulfates or combinations of these materials; or organic materials including biopolymers selected from collagen, gelatin, hyaluronic acid or chemically derived modifications of hyaluronic acid, chitin, chitosan or chitosan derivatives, fibrin, dextran, agarose, or calcium alginate; or synthetic polymeric materials such as polylactic acid, polyglycolic acid or copolymers or combinations of the two, polyurethanes, polycarbonates, polycaprolactones, hydrogels such as polyacrylates, polyvinyl alcohols, polyethylene glycols, or polyethyleneimines; or particles of tissues selected from bone or demineralized bone, cartilage, tendon, ligament, fascia, intestinal mucosa or other connective tissues, or chemically modified derivatives of these materials.

21. The method of Claim 18 wherein the scaffold has been shaped to configure the geometry of the area of the body receiving the cells for implantation.

22. The method of Claim 18 wherein the scaffold is shaped to produce a form that can be cut or modified to a desired shape at the time of implantation.

23. The method of Claim 1 wherein the cells in the injectable formulation are chondrocytes.

24. The method of Claim 1 wherein the cells in the injectable formulation are extracellular matrix producing cells selected from chondrocytes; osteoblasts; keratinocytes; fibroblasts derived from skin, tendon, ligament, meniscus, temporalmandibular joint or intervertebral joint, disk or any other connective tissue; stem cells derived from bone marrow stroma, muscle, skin or other stem cell-containing tissue; embryonic stem cells; or combinations of these cells that may be seeded onto the microcarrier.

25 .The method of Claim 1 wherein the injectable formulation is made by cells in a solution suitable for injection.

26. The method of Claim 1 wherein the injectable formulation is made by culturing cells on biodegradable microcarriers.

27. The method of Claim 26 wherein the microcarrier is selected from inorganic materials, organic materials including biopolymers, synthetic polymeric materials, or chemically modified derivatives of these materials.

28. The method of Claim 26 wherein the microcarrier is selected from inorganic materials selected from calcium phosphates, calcium carbonates, calcium sulfates or combinations of these materials; organic materials including biopolymers selected from collagen, gelatin, hyaluronic acid or chemically derived modifications of hyaluronic acid, chitin, chitosan or chitosan derivatives, fibrin, dextran, agarose, or calcium alginate; synthetic polymeric materials such as polylactic acid, polyglycolic acid or copolymers or combinations of the two, polyurethanes, polycarbonates, polycaprolactones, hydrogels selected from polyacrylates, polyvinyl alcohols, polyethylene glycols,

or polyethyleneimines; or particles of tissues such as bone or demineralized bone, cartilage, tendon, ligament, fascia, intestinal mucosa or other connective tissues, or chemically modified derivatives of these materials.

29. The method of Claim 26 wherein the injectable formulation is a fluid medium suitable for injection selected from: isotonic saline for injection, phosphate buffered saline, or Hank's balanced salt solution.

30. The method of Claim 26 wherein the fluid medium suitable for injection contains a material capable of polymerizing or gelling after implantation.

31. The method of Claim 30 wherein the material is selected from fibrin glues, collagen, combinations of fibrin/collagen, hyaluronic acid, calcium alginate gels, chitosan derivatives capable of gelling at body temperature, hydrogels such as polyacrylates, polyvinyl alcohols, polyethylene glycols, or polyethyleneimines.

32. The method of Claim 26 wherein the fluid medium suitable for injection contains a bioactive factor.

33. The method of Claim 32 wherein the bioactive factor is selected from cytokines, growth factors, antibodies, adhesion factors or integrins.

34. The method of Claim 32 wherein the bioactive factor is selected from TGF-β, BMPs, PDGF, FGFs and interleukins.

35. The method of Claim 30 wherein the *in situ* gelling of these materials is initiated by thermal, enzymatic or chemical catalysts, pH or ionic strength changes or photo-initiation procedures.

36. A method for replacing a tissue or body part or filling a void in a tissue comprising (1) preparing a solid implant; (2) preparing an injectable cell-containing formulation; (3) implanting the solid implant into a cavity or defect in the tissue; and (4) injecting the injectable cell-containing formulation into the interstices between the tissue and the solid implant.

37. The method of Claim 36 in which the solid implant contains cells.

38. The method of Claim 36 wherein the cells are chondrocytes.

39. The method of Claim 36 wherein the cells are selected from chondrocytes; osteoblasts; keratinocytes, fibroblasts derived from skin, tendon, ligament, meniscus, disk or any other connective tissue; stem cells derived from bone marrow stroma, muscle, skin or other stem cell-containing tissue; embryonic stem cells; or combinations of these cells that may be seeded onto the microcarrier.

40. The method of Claim 37 wherein the cells used to prepared the solid implant differ from the cells used to prepare the injectable cell-containing formulation.

41. The method of Claim 37 wherein the solid cell-containing implant is prepared by culturing cells on a solid scaffold.

42. The method of Claim 37 wherein the solid cell-containing implant is prepared by culturing cells on microcarrier particles.

43. The method of Claim 36 wherein the injectable cell-containing formulation is prepared by culturing cells on microcarrier particles.

44. The method of Claim 36 wherein the injectable cell-containing formulation comprises a suspension of cells in a medium suitable for injection.

45. A method for replacing a tissue or body part or filling a void in a tissue comprising (1) preparing a solid cell-containing implant from cells; (2) preparing an injectable cell-containing formulation of cell-microcarrier aggregates; (3) coating the surface of the cavity or lesion of the tissue with the injectable cell-containing formulation; and (4) implanting the solid cell-containing implant into the cavity or lesion such that it is in contact with the injectable cell-containing formulation.

46. The method of claim 45 wherein the cells are chondrocytes.

47. The method of claim 45 wherein the cells are selected from chondrocytes; osteoblasts; fibroblasts derived from skin, tendon, ligament, meniscus, disk or any other connective tissue; stem cells derived from bone marrow stroma, muscle, skin or other stem cell-containing tissue; embryonic stem cells; or combinations of these cells that may be seeded onto the microcarrier.

48. The method of Claim 45 wherein the cells used to prepared the solid implant differ from the cells used to prepare the injectable cell-containing formulation.

49. The method of Claim 45 wherein the solid cell-containing implant is prepared by culturing cells on a solid scaffold.

50. The method of Claim 45 wherein the solid cell-containing implant is prepared by culturing cells on microcarrier particles.

51. The method of Claim 45 wherein the injectable cell-containing formulation is prepared by culturing cells on microcarrier particles.

52. The method of Claim 45 wherein the injectable cell-containing formulation comprises a suspension of cells in a medium suitable for injection.

53. The method of replacing a tissue or body part or filling a void in the head or neck area comprising the steps of obtaining a non-diseased, cell sample from the respective patient's head and neck area, rapidly growing additional cells obtained from said cell sample in a bioreactor to produce a suspension of cell-microcarrier aggregates, and further culturing some of the cell-microcarrier aggregates within a predetermined mold which is the mirror image of the patient's tissue, body part or void, such that a molded tissue or body part is produced, and surgically implanting the molded tissue or body part in combination with an injectable suspension of cell-microcarrier aggregates as a replacement in the patient's head and neck area, such that the implanted tissues regenerates therein and fuses with the adjacent tissues in the head and neck area of the respective patient.

54. An implant for a cavity in the body of a patient, comprising a formed aggregation of cells on first microcarrier particles which approximates the size and shape of the cavity in the patient's body, and an interface layer of cells between the formed aggregation of cells and the cavity in the patient's body, wherein the formed aggregation of cells are implanted in a substantially solid form following culturing of the cells on the micro carrier particles during a first time period, and wherein

the interface layer of cells have been cultured on second microcarrier particles during a second time period which is substantially shorter than the first time period and have been applied while in a substantially fluid state.

55. The implant of claim 54, wherein the cells on the formed aggregation of cells comprises chondrocytes, thereby resulting in an implant having cartilage properties.

56. The implant of claim 55, wherein the formed aggregation of cells comprises a molded aggregation of cells.

57. The implant of claim 54, wherein the interface layer of cells comprises cultured stem cells, thereby promoting the rapid integration of the formed aggregation of cells into the soft tissue, muscle or bone surrounding the body cavity.

58. The implant of claim 57, wherein the cultured stem cells are capable of producing cells selected from the group consisting of fibroblastic, myoblastic or osteoblastic phenotype cells.

59. The implant of claim 54, wherein the interface layer of cells is injected into the body cavity prior to the implantation of the formed aggregation of cells therein.

60. The implant of claim 54, wherein the interface layer of cells is injected into the body cavity after the implantation of the formed aggregation of cells therein.

61. The implant of claim 54, wherein the interface layer of cells is coated onto the formed aggregation of cells, and then the coated formed aggregation of cells is implanted into the body cavity.

62. The method of making an implant for insertion into the body cavity of a patient, comprising the steps of forming a sintered aggregation of cells cultured on first microcarrier particles during a first time period, such that the sintered aggregation is in a substantially solid state, forming a plurality of cells on second microcarrier particles during a second time period which is shorter than the first time period, such that the plurality of cells on the second microcarrier particles is in a substantially fluid state, and combining the sintered aggregation of cells and the substantially-fluid plurality of cells to make the implant.

63. The method of claim 62, wherein the sintered aggregation of cells approximates the size and shape of the body cavity, and wherein the substantially-fluid plurality of cells forms an interface layer between the body cavity and the sintered aggregation of cells.

64. The method of claim 63, wherein the substantially-fluid plurality of cells is injected into the body cavity after the sintered aggregation of cells is inserted into the body cavity.

65. The method of claim 63, wherein the substantially-fluid plurality of cells is injected into the body cavity before the sintered aggregation of cells is inserted into the body cavity.

66. The method of claim 63, wherein the substantially-fluid plurality of cells forms a coating on the sintered aggregation of cells before the sintered aggregation of cells is inserted into the body cavity.

67. The method of claim 62, wherein the cells comprise chondrocytes.

68. The method of claim 62 wherein the cells are selected from chondrocytes; osteoblasts; fibroblasts derived from skin, tendon, ligament, meniscus, disk or any other connective tissue; stem cells derived from bone marrow stroma, muscle, skin or other stem cell-containing tissue; embryonic stem cells; or combinations of these cells that may be seeded onto the microcarrier.

69. The method of Claim 62 wherein the microcarrier is selected from inorganic materials selected from calcium phosphates, calcium carbonates, calcium sulfates or combinations of these materials; organic materials including biopolymers selected from collagen, gelatin, hyaluronic acid or chemically derived modifications of hyaluronic acid, chitin, chitosan or chitosan derivatives, fibrin, dextran, agarose, or calcium alginate; synthetic polymeric materials such as polylactic acid, polyglycolic acid or copolymers or combinations of the two, polyurethanes, polycarbonates, polycaprolactones, hydrogels selected from polyacrylates, polyvinyl alcohols, polyethylene glycols, or polyethyleneimines; or particles of tissues such as bone or demineralized bone, cartilage, tendon, ligament, fascia, intestinal mucosa or other connective tissues, or chemically modified derivatives of these materials.

70. Method of treating a lesion on or in the skin comprising filling said lesion with a solid cell-containing implant along with an injectable cell-containing formulation.